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# Successful Treatment of Lymphomatoid Granulomatosis Using Cyclosporin-A After Failure of Intensive Chemotherapy

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**We report the successful and maintained response of lymphomatoid granulomatosis using a new approach to therapy, cyclosporin-A, after failure of aggressive multiagent chemotherapy.** © 1996 Wiley-Liss, Inc.

**Key words: lymphomatoid granulomatosis, angiocentric immunoproliferative lesion, lung lymphoma, cyclosporin-A, postthymic T-cell lymphoma, malignant lymphoma**

## INTRODUCTION

Lymphomatoid granulomatosis, first described by Liebow and associates in 1972 [1], is a rare immunoproliferative disorder better classified today as an angiocentric immunoproliferative lesion (AIL). It is characterized by an angioinvasive and angiodestructive lymphoreticular infiltrate mainly composed of T lymphocytes, affecting most frequently the lungs. Long-term remissions are rare, with mortality close to 60% the first year and median survival of 14 months from the time of diagnosis regardless of the treatment employed [2]. We report a case of successful and maintained response of lymphomatoid granulomatosis to a new approach to therapy, Cyclosporin-A, after failure of aggressive multiagent chemotherapy.

## CASE REPORT

The patient is a 51-year-old Caucasian man, nonsmoker, who presented to his local physician complaining of progressive shortness of breath. Chest X-ray and CT scan of the chest revealed multiple bilateral mixed nodular and interstitial infiltrates without lymphadenopathy. Sputum collection, bronchoscopy, bone scan, bone marrow biopsy, abdominal CT scan, and blood tests failed to establish a diagnosis. His condition rapidly deteriorated despite empiric antibiotic therapy and he required endotracheal intubation and ventilatory support. An open lung biopsy was then performed which yielded the diagnosis of lymphomatoid granulomatosis (Fig. 1) classified as a grade II angioimmunoproliferative lesion (AIL) using the criteria established by Lipford et al. [3]. Immunohistochemistry showed that the cells, small and medium size lymphocytes, were T cells (DAKO-CD45RO+, UCHL 1 Dako, Carpinteria, CA).

He was treated with PRoMACE-MOPP, an intensive multiagent chemotherapy regimen utilizing eight drugs, used for the treatment of aggressive lymphomas. The pulmonary infiltrates cleared over a period of 1 month and he continued the chemotherapy, completing six full cycles and complicated by an episode of neutropenic sepsis. His chest X-ray was normal when chemotherapy was discontinued. Approximately 1 month later he again developed progressive shortness of breath and the evaluation revealed recurrence of the lymphomatoid granulomatosis (Fig. 2).

Cyclosporin-A was considered for salvage therapy because of its relatively selective activity against T (CD4+) lymphocytes. The potential risks and benefits were discussed with the patient and his wife and informed consent was obtained. The treatment was started with 500 mg per

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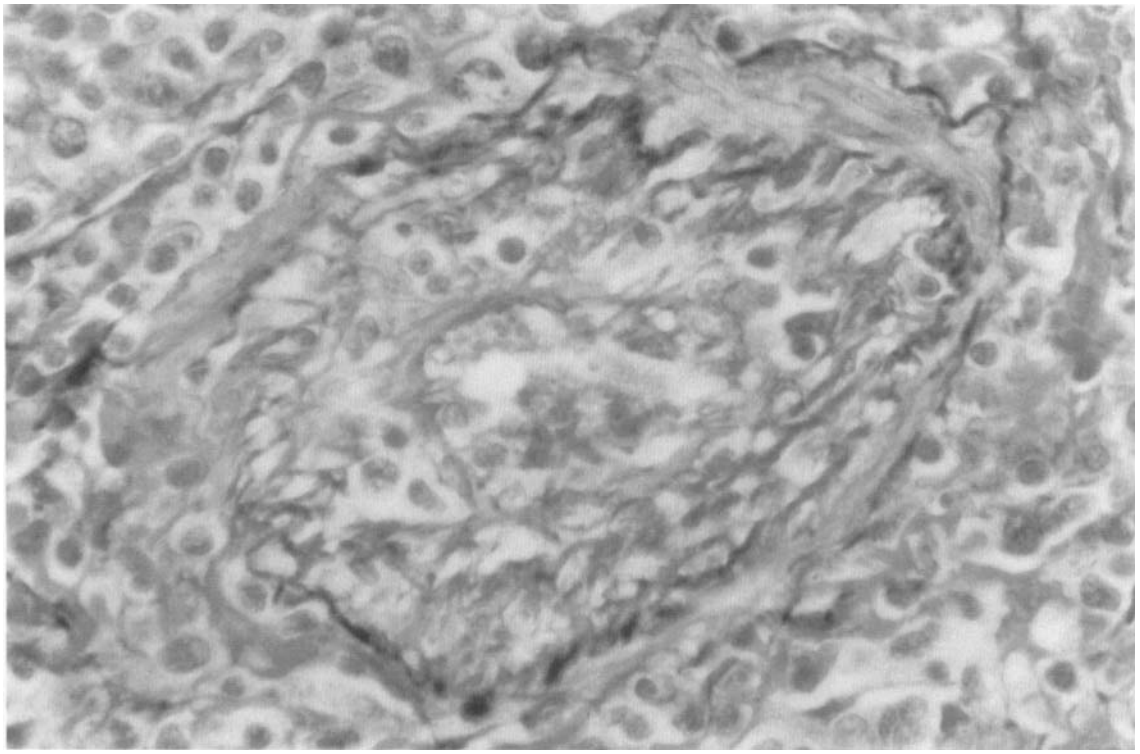

Fig. 1. Angioinvasion with angiodestruction was a feature of the lesion, best demonstrated by special stains. Verrof elastic tissue stain counterstained with van Gieson, ×200.

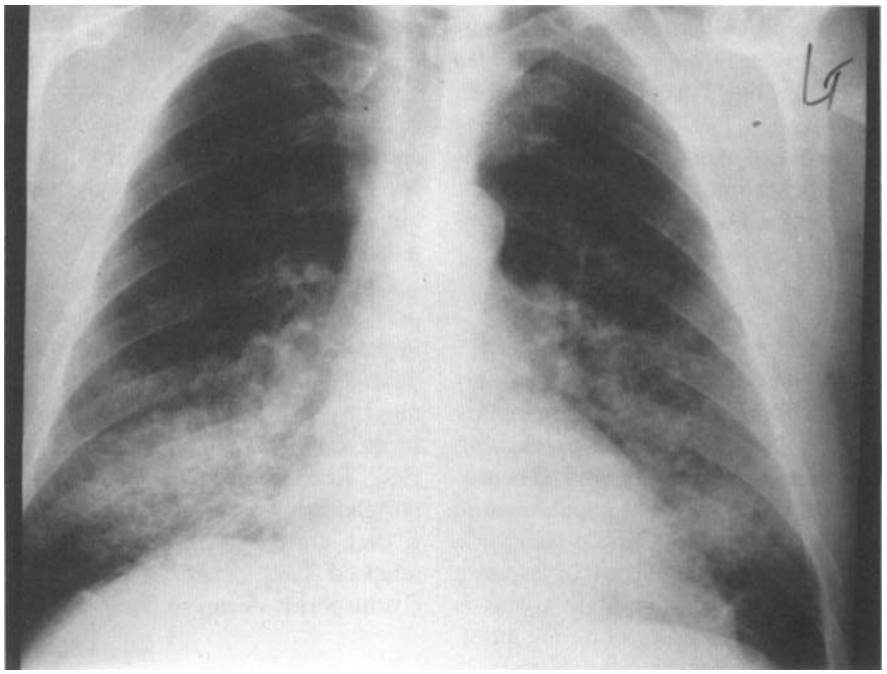

Fig. 2. Bilateral diffuse nodular and intersticial infiltrates showing recurrence of the tumor 1 month after chemotherapy finished.

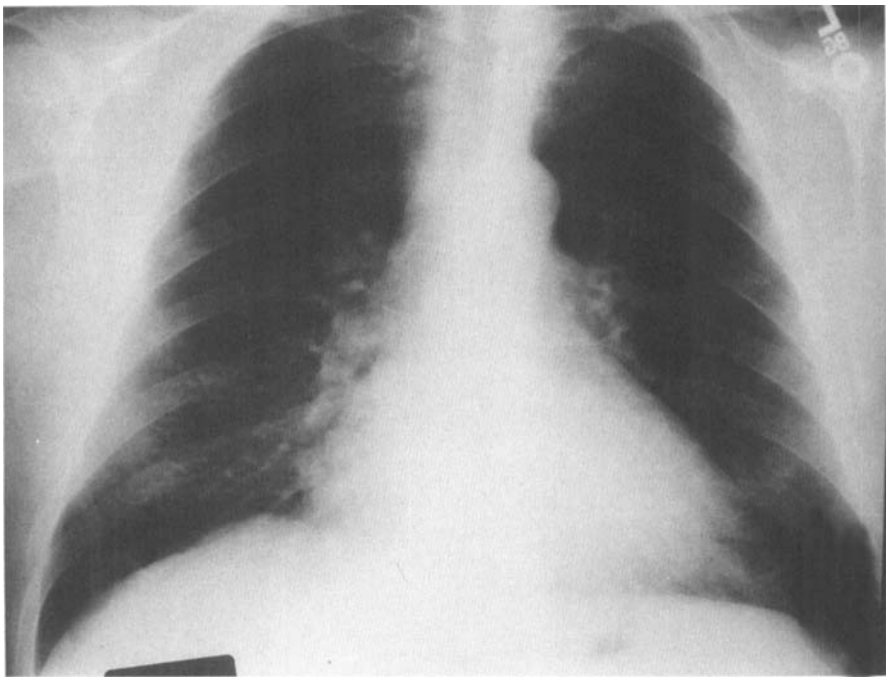

**Fig. 3. Showing remission of the bilateral nodular infiltrates after the treatment was started with Cyclosporine A.**

day for the first 3 months, and reduced to 300 mg per day thereafter. Symptomatic improvement as well as radiographic clearing was evident within 4 weeks, the pulmonary infiltrates completely resolved within 8 weeks (Fig. 3).

The patient remained in remission for 2 years taking 300 mg per day of Cyclosporin-A. Concerns about cumulative toxicity and chronic immunosuppression prompted discontinuation of the drug, but 3 weeks later he again developed progressive dyspnea. Evaluation confirmed recurrence of the disease. Cyclosporin-A therapy was reinstituted and he again cleared his pulmonary infiltrates. He remains in clinical remission, on daily Cyclosporin-A, 4 years after the initial diagnosis was established.

## DISCUSSION

Lymphomatoid granulomatosis results from a proliferation of atypical lymphoreticular cells predominantly composed of T (CD4+, CD45RO+) lymphocytes, with a predilection for pulmonary, cutaneous, renal, and neurological involvement [4–9]. The etiology of lymphomatoid granulomatosis is not known, although Epstein-Barr virus has been implicated in some cases [10,11]. Initial response to therapy using costicosteroids and cytotoxic agents is usually prompt and dramatic but remissions are brief. Resistance to therapy ultimately develops and death most commonly results from respiratory failure or secondary infections. Patients classified as angioimmunoproliferative lesions type II, as our patient, have a very poor prognosis with 67% developing malignant lymphoma 1 year after diagnosis is done [3].

Survival has not increased significantly despite the use of intensive chemotherapeutic regimes such as those used in the treatment of aggressive non-Hodgkin's lymphomas [2,12,13].

Cyclosporin-A is a neutral hydrophobic cyclic polypeptide of fungal origin. It is a potent immunosuppressive agent with relatively selective activity against helper (CD4) T-lymphocytes. It interferes with the production and release of interleukin-2, interferon-gamma, and B-cell growth factor [14]. Other reported effects include binding of the cytosolic protein cyclophilin found in high levels in some lymphomas [15].

Cyclosporin-A has been widely used as an immunosuppressive agent in transplantation for many years. Also, in the last 10 years Cyclosporin-A has been used in the treatment of some patients with cutaneous T-cell lymphomas (mycosis fungoides and Sezary syndrome) with some success [16,17] but responses lasted 6 months or less [18]. Recently sixteen patients with refractory T-cell lymphomas were treated with Cyclosporine-A in a phase II trial. Only two patients responded but both promptly relapsed [19]. There are no reports of the use of Cyclosporine-A in lymphomatoid granulomatosis.

## CONCLUSION

This case suggests that Cyclosporin-A might be effective as a therapeutic option in the treatment of lymphoma-

toid granulomatosis with fewer adverse effects and better survival compared to conventional and aggressive chemotherapy. Further study is required to define its place in the management of this rare disorder.

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